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SYNTHESIS OF ROBUSTIC ACID

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A number of naturally occurring 3-phenyl-4-hydroxycoumarins have isopentenylated units either in the acyclic or heterocyclic or both the forms.[1] They are scandenin, lonchocarpic acid and lonchocarpenin isolated from the roots of Derris scandens[2,3] and derrusnin, robustic acid, methyl robustate, robustin and 4-O-methyl robustin from D. robusta.[4,5] Since isopentenylation may occur in Nature either at the coumarin stage or before the formation of the coumarin ring, both the approaches are explored to synthesize some of the natural compounds.

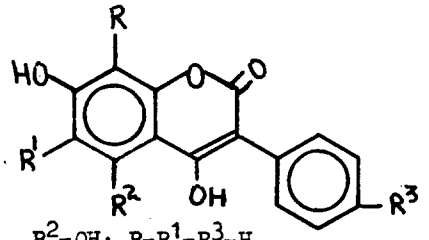
First 3-phenyl-4,5,7-trihydroxycoumarin[6] (I) was prenylated with prenyl bromide in the presence of methanolic methoxide giving a mixture from which two pure compounds could be isolated by coloumn chromatography. One of them (m.p.167-68°) was indicated as tetra-C-prenyl derivative by its elemental analysis and NMR spectrum. Since its I.R. spectrum showed intact coumarin ring (ν_{CO} 1685cm^{-1}) and NMR spectrum had no aromatic proton signal of the ring A, it was concluded that all prenyl units are in ring A and the compound has structure (II). The other product (m.p.180-81°) proved to be a tri-C-prenyl coumarin derivative again on the basis of analysis, NMR and I.R. spectra. Its structure could be (III) which is supported by the presence of one singlet at δ 5.86ppm in its NMR spectrum. A parallel series of experiments with 3-phenyl-4'-methoxy-4,5,7-trihydroxycoumarin (IV) revealed similar results; tetra-C-prenyl-(V, m.p.146-47°) and tri-C-prenyl-(VI, m.p. 171-72°) derivatives formed. Thus it appears that 3-phenyl-4,5,7-trihydroxycoumarins behave differently from 5,7-dihydroisoflavonoid system[7] in which no gem prenylation occurs but it is more like phloroisovalerophenone[8] Probably the coumarin ring opens up and undergoes polyprenylation like phloroacylophenone followed by ring closure giving poly-C-prenyl coumarins.

Hence this approach does not seem to be feasible for the synthesis of natural isopentenylated 3-phenyl-4-hydroxycoumarins.

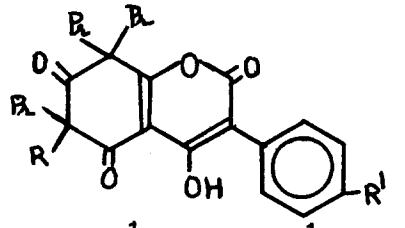
The second approach consisting of prenylation at the desoxybenzoin stage and subsequent coumarin ring formation was then investigated. Acyclic 3-C-(VII) and 5-C-(VIII)prenyl derivatives of 2,4-dihydroxyphenyl benzyl ketone and their oxidatively cyclised products(IX) and (X), respectively prepared earlier[10] were examined for their conversion into corresponding 3-phenyl-4-hydroxycoumarins by condensing with ethylchloroformate in the presence of potassium carbonate and acetone. In each case the coumarins formed(XI,m.p.208-9°;XII,m.p.247-48°;XIII,m.p.222-23°; XIV,m.p.228-29° respectively) and their structures were confirmed by NMR,UV and I.R. spectra. Thus this approach is feasible and hence now adopted for the synthesis of natural robustic acid (XXVI).

2,4-Dihydroxy-6-methoxyphenyl-4-methoxybenzyl ketone[7](XV)was subjected to nuclear prenylation with (i) 2-methyl but-3-en-2-ol in the presence of BF_3-etherate as well as (ii) prenyl bromide in the presence of methanolic potash. In the first case, only two pure compounds (m.p.153-54°;and 91-92°) could be obtained by column chromatography. Both of them were found to be mono-C-prenyl derivatives on the basis of elemental analysis and NMR spectra showing one doublet of two protons in each case at δ 3.35ppm(J=7Hz). Obviously one is 3-C-prenyl-(XVI) and the other is 5-C-prenyl-(XVII)derivative. The compound(m.p.153-54°) which on direct treatment with formic acid gave two chromans[4](XVIII,m.p.120-21° and XIX, m.p.149-50°) but after partial methylation to(XX,m.p.94-95°) and subsequent treatment with formic acid gave only one chroman[4](XXI,m.p.104-5°)was assigned 3-C-prenyl structure(XVI). On the other hand, the compound(m.p.91-92°)which gave only one chroman[4](XXII,m.p. 114-15°) on direct cyclisation with formic acid but no chroman after partial methylation and subsequent formic acid treatment, was given 5-C-prenyl structure(XVII).

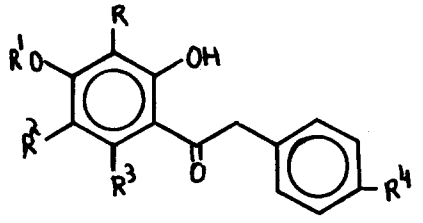
In the second method of prenylation, column chromatography of the product afforded three crystalline compounds. The first major compound(m.p.153-54°)was identified as 3-C-prenyl derivative(XVI);the second minor component(m.p.85-87°) as p-methoxy phenyl acetic acid which could have formed as a result of facile cleavage of the starting desoxybenzoin; and the third minor component(m.p.



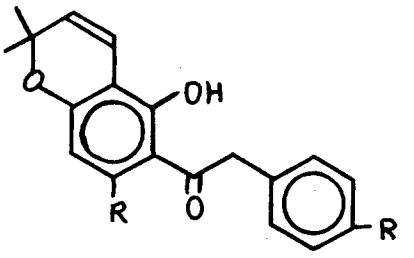
I, R^2=OH; R=R^1=R^3=H
IV, R^2=OH; R^3=OMe; R=R^1=H
XI, R =Pr; R^1=R^2=R^3=H
XII, R^1=Pr; R =R^2=R^3=H



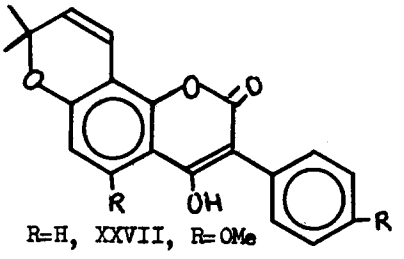
II, R=Pr; R^1=H; III, R=R^1=H
V , R=Pr; R^1=OMe; VI, R=H; R^1=OMe



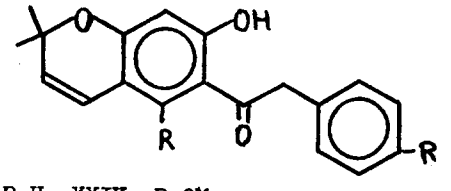
VII, R=Pr; R^1=R^2=R^3=R^4=H
VIII, R^2=Pr; R=R^1=R^3=R^4=H
XV, R^3=R^4=OMe; R=R^1=R^2=H
XVI, R=Pr; R^1=R^2=H; R^3=R^4=OMe
XVII, R^2=Pr; R=R^1=H; R^3=R^4=OMe
XX, R=Pr; R^1=Me; R^2=H; R^3=R^4=OMe
XXIII, R^1=Pr; R=R^2=H; R^3=R^4=OMe



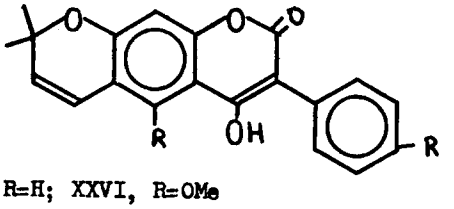
IX, R=H; XXV, R=OMe



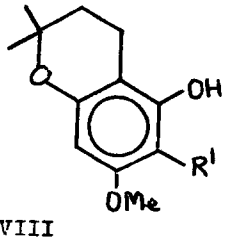
XIII, R=H, XXVII, R=OMe



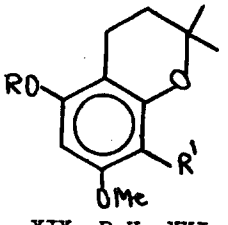
X, R=H; XXIV, R=OMe



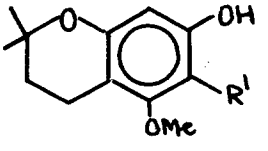
XIV, R=H; XXVI, R=OMe



XVIII



XIX, R=H; XXI, R=Me



XXII

For XVIII, XIX, XXI, XXII, R^1=-CO-CH_2-p-anisyl

76-77°) as 4-prenyl ether (XXIII)as follows. NMR showed a doublet of two protons at δ 4.5ppm(J=9Hz) and it was identical with an authentic sample prepared by prenylation of the desoxybenzoin(XV) with one mole of prenyl bromide in the presence of potassium carbonate and acetone.

Both 5-C-prenyl-(XVII)and 3-C-prenyl-(XVI) desoxybenzoins were separately cyclised with DDQ, when the corresponding phenacyl chromenes(XXIV,m.p.86-87°;XXV, m.p.155-56° respectively) resulted. Both the structures were supported by their NMR spectra in $CDCl_3$;for XXIV δ:1.42ppm(1s,6H,$(CH_3)_2C<$), 3.79(1s,6H,2 OCH_3groups) 4.32(1s,2H,CO-CH_2-),5.62 and 6.53(2d,J=10 Hz,2H,-CH=CH-),6.21(1s,1aromatic H at 8 position) and 6.88 and 7.21ppm(2d,J=8 Hz,4 aromatic H at 2',3',5' and 6' positions);for XXV δ:1.42(1s,6H,$(CH_3)_2C<$),3.77 and 3.82(2s,6H,2-OCH_3),4.22(1s,2H, CO-CH_2-),5.42 and 6.65(2d,J=10 Hz,2H,CH=CH-),5.88(1s,1 aromatic H at 8 position) and 6.82,7.14ppm(2d,J=8 Hz,4 aromatic H at 2',3',5' and 6' positions).

Both the above chromenes(XXIV) and (XXV) were finally converted into their corresponding 3-phenyl 4-hydroxycoumarins(XXVI)and(XXVII) by treatment with ethyl chloroformate in the presence of potassium carbonate and acetone. The former (XXVI ,m.p.208-9°) was found to have all the properties of natural coumarin, robustic acid.
The latter (XXVII, m.p.220-21°) could be named as isorobustic acid.

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